



**QUEEN'S
UNIVERSITY
BELFAST**

Vaccination and All Cause Child Mortality 1985-2011: Global Evidence from the Demographic and Health Surveys

McGovern, M. E., & Canning, D. (2015). Vaccination and All Cause Child Mortality 1985-2011: Global Evidence from the Demographic and Health Surveys. *American Journal of Epidemiology*, 182(9), 791-798.
<https://doi.org/10.1093/aje/kwv125>

Published in:
American Journal of Epidemiology

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
[Link to publication record in Queen's University Belfast Research Portal](#)

Publisher rights

© The Author 2015. Published by Oxford University Press on behalf of the Johns Hopkins Bloomberg School of Public Health. This is a pre-copyedited, author-produced PDF of an article accepted for publication in *American Journal of Epidemiology* following peer review. The version of record- McGovern, ME & Canning, D 2015, 'Vaccination and All Cause Child Mortality 1985-2011: Global Evidence from the Demographic and Health Surveys' *American Journal of Epidemiology*, vol 182, no. 9, pp. 791-798., is available online at: <http://aje.oxfordjournals.org/content/182/9/791.abstract?sid=7b8194b4-f4f0-42e3-b42b-77bb03dc45d0>

General rights

Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

Vaccination and All Cause Child Mortality 1985-2011: Global Evidence from the Demographic and Health Surveys*

Mark E. McGovern[†] David Canning[‡]

February 2015

Abstract

Based on models with calibrated parameters for infection, case fatality rates, and vaccine efficacy, basic childhood vaccinations have been estimated to be highly cost effective. In this paper, we estimate the association of vaccination with mortality directly from survey data. Using 149 cross-sectional Demographic and Health Surveys, we determine the relationship between vaccination coverage and under five mortality at the survey cluster level. Our data include approximately one million children in 68,490 clusters in 62 countries. We consider the childhood measles, Bacille Calmette-Guérin (BCG), Diphtheria-Pertussis-Tetanus (DPT), Polio, and maternal tetanus vaccinations. Using modified Poisson regression to estimate the relative risk of child mortality in each cluster, we also adjust for selection bias caused by the vaccination status of dead children not being reported. Childhood vaccination, and in particular measles and tetanus vaccination, is associated with substantial reductions in childhood mortality. We estimate that children in clusters with complete vaccination coverage have relative risk of mortality 0.73 (95% Confidence Interval: 0.68, 0.77) that of children in a cluster with no vaccination. While widely used, basic vaccines still have coverage rates well below 100% in many countries, and our results emphasize the effectiveness of increasing their coverage rates in order to reduce child mortality.

JEL Classification: *J10, I10*

Keywords: *Vaccinations, Child Mortality, Missing Data, Measles, Bacille Calmette-Guérin, Diphtheria-Pertussis-Tetanus, Polio, Tetanus*

*We are grateful to seminar participants at Harvard and two anonymous referees for comments. This project received financial assistance from the Bill & Melinda Gates Institute for Population and Reproductive Health, and the Program on the Global Demography of Aging and the National Institutes of Health [grant no. 1 P30 AG 024409-09].

[†]Corresponding author. Email: mcgovern@hsph.harvard.edu. Harvard Center for Population and Development Studies, and Department of Global Health and Population, Harvard T.H. Chan School of Public Health. Address: 9 Bow Street, Cambridge, MA 02138, USA.

[‡]Email: dcanning@hsph.harvard.edu. Harvard Center for Population and Development Studies, and Department of Global Health and Population, Harvard T.H. Chan School of Public Health.

1 Introduction

There is evidence that vaccines are effective in children against specific diseases such as tuberculosis (Colditz et al., 1994), measles (Goldhaber-Fiebert et al., 2010), and tetanus (Koenig et al., 1998; Van Den Ent et al., 2011), and increases in vaccine coverage have therefore been seen as an important strategy for reducing infant and child mortality (Feikin et al., 2015). There have been a series of coordinated global efforts to increase immunization rates in developing countries as a means of achieving improvements in child health, including the Expanded Program on Immunization (EPI), initiated in 1974, and the Global Alliance for Vaccines and Immunization (GAVI), initiated in 2000 (Brenzel et al., 2006). The period from 2010-2019 has been termed the “Decade of Vaccines” (Stack et al., 2011). Largely due to donor funds, the coverage of vaccination (as measured by the proportion of children receiving three doses of the diphtheria-tetanus-pertussis vaccine by 12 months of age - DPT3) increased substantially, from 5% or less in 1974, to 75% in 1990, to 84% in 2013, albeit with important regional, national, and sub-national variation in achieved coverage (Burton et al., 2009; Harris et al., 2014). Increases in coverage in Africa were achieved with a series of supplementary immunization activities (SIA) in the late 1990s, which were successful in reaching 24 million children between 1996 and 2000 (Biellik et al., 2002).

Almost 20 million children failed to receive DPT3 in 2010, a third of whom were in Africa, and mainly concentrated in 10 countries (Bosch-Capblanch et al., 2012). In addition, other vaccines have lower levels of coverage, with much lower rates for measles than for DPT3. While the numbers of vaccine-preventable deaths are large, the proportion of deaths caused by vaccine-preventable diseases appears to be relatively small, for example, measles accounted for 4% of all childhood deaths under the age of five in the period 2000-2003, while tetanus accounted for a further 7%, with much smaller impacts from the other diseases (Bryce et al., 2005). These figures had reduced even further by 2008 (Black et al., 2010). Nevertheless, studies of the cost effectiveness of vaccination using only the effect on disease specific mortality find it highly cost effective (Bishai et al., 2011).

However, there is potential for routine vaccines to have an impact above and beyond the expected association with the specific disease. For example, the introduction of the measles vaccine in some African communities in the 1980s led to a far greater reduction in overall child mortality than would be expected from reductions in measles mortality alone (Aaby et al., 1984). Similar large effects of all-cause mortality were found after the introduction of measles vaccination in Matlab, Bangladesh (Aaby et al., 2003; Clemens

et al., 1988; Koenig et al., 1998). These findings have been replicated in other settings, including in Randomized Control Trials (RCTs) (Aaby et al., 2010, 1995; Holt et al., 1990). There is also some evidence that the Bacillus Calmette-Gurin (BCG) is protective against neonatal mortality, and some suggestion that DPT vaccination may increase mortality in some settings (Aaby et al., 2012, 2004a). The hypothesis that vaccines have non-specific effects on mortality has received validation in animal studies demonstrating a plausible mechanism for these effects. Administration of BCG vaccine in mice led to trained immunity via epigenetic reprogramming (Kleinnijenhuis et al., 2012).

Despite recent progress in reducing under five mortality (Liu et al., 2012), there has been a renewed focus on implementing interventions to allow countries to reach the target of a reduction in child mortality of two thirds from its 1990 level as set by the fourth Millennium and Development Goal (MDG). Immunization may provide a highly cost effective mechanism for further reducing child mortality. However, many studies on vaccine cost effectiveness rely on calibration studies and simulation exercises, with measures of the association between vaccination status and mortality often taken from specific cohorts in localized areas (Bishai et al., 2011; Verguet et al., 2013). There are likely to be important differences both across and within countries in terms of the effectiveness of vaccination. One issue is how vaccines are administered, a factor which could potentially affect vaccine efficacy. For example, there is substantial variation in the timing of vaccination in low and middle income countries (Clark and Sanderson, 2009). A second issue is that actual vaccine effectiveness may be lower in practice in large scale implementation than in small scale studies (Uzicanin and Zimmerman, 2011), due to failures of the cold chain, storage, and handling. A third issue is that the effectiveness of vaccination in reducing child mortality may depend on other factors, for example their family's socio-economic status and the child's nutrition (Koenig et al., 2001), making the average effectiveness in a population differ from that found in small studies.

From a policy perspective, it is important to understand whether previous findings from RCTs and observational studies based on specific cohorts can be generalized to diverse populations who experience different levels of economic development, disease environment, and health care systems (Sachdev, 2014). With some exceptions (Aaby et al., 1995), relatively few previous studies have examined the relationship between basic childhood vaccines and all-cause mortality with population-based data in more than a limited number of countries; most past studies have relied on data from a single location. The advantage of our approach is that we use nationally representative data from multiple countries that reflect a wide variety of populations and are likely to have good external validity (Fink et al., 2011). Our data have information on all basic

vaccines, and mortality data up to five years of age. Our methodological contribution is that we introduce a correction for potential selection bias induced by missing data on children who have died.

This paper uses information from a large number of developing countries using Demographic and Health Surveys (DHS) to examine the relationship between cluster level vaccination coverage and cluster level under five mortality. We focus on the association between all-cause mortality and the measles, Bacille Calmette-Guérin (BCG), DPT, Polio and maternal tetanus vaccinations, while controlling for the cluster’s socio-economic and demographic characteristics. The goal of this paper is to establish the relationship between mortality and immunization in population based data. Given recent findings in the literature, we hypothesize larger impacts of the basic childhood vaccines than would be expected from their association with cause specific mortality alone.

2 Methods

2.1 Data

We combined all publicly available datasets from the DHS for which we were able to measure child mortality, the vaccination status of living children for all five basic vaccines, and household wealth (which is based on an asset index). The DHS are nationally representative samples, typically of those aged 15-49, in developing countries which have been conducted since 1980 ([Corsi et al., 2012](#); [Fabic et al., 2012](#); [Hancioglu and Arnold, 2013](#)). Detailed birth histories are collected from women documenting all children born in the previous five years, together with the current status of these children (Fink et al., 2011). Our sample includes around 1 million births in 62 countries and 149 surveys, born between 1985 and 2011. Most DHS surveys include vaccination status for one dose of BCG, DPT 1-3, Polio 1-3, one dose of measles, and maternal tetanus.

We excluded surveys from DHS round 1 as in the first wave vaccination status was typically recorded from vaccination cards alone, resulting in a high proportion of missing values, whereas later surveys include the mother’s report of their children’s vaccination status. Overall, 13% of children in the sample are reported as not having a card, while a further 30% do not have their card presented to the interviewer. If the vaccination card is not available, mothers are asked to report vaccination status. We define vaccination status according to either the vaccination card, or when unavailable, as reported by the mother. Langsten and Hill show that maternal reporting of BCG status in Egypt is 98% accurate, compared to 83% for DPT3 ([Langsten](#)

and Hill, 1998). More recently, Murray and colleagues do not find any evidence that maternal recall bias affects coverage estimates in the DHS (Murray et al., 2003). However, the mother-reported information is an important limitation to the data (Cutts et al., 2013).

World Health Organization (WHO) recommendations for vaccination have changed over time, in part reflecting updated evidence on the effectiveness of vaccines, and changing priorities from variation in coverage rates. For example, initially the EPI recommended one dose of measles containing vaccine (MCV1), however two doses are now standard in many countries as vaccination failure typically occurs in 10-15% of infants receiving the first dose at 9 months (World Health Organization, 2009). Failure rates are likely to be even higher if immunization occurs before 9 months due to immaturity of the immune system. The WHO recommends prioritizing the first measles dose until 80% coverage of MCV1 for three consecutive years has been achieved (World Health Organization, 2009). Regarding Polio, in high risk countries an Oral Polio Vaccine (OPV) birth dose (Polio 0) followed by a primary series of three OPV doses and at least one Inactivated Poliovirus Vaccine (IPV) dose is now recommended (World Health Organization, 2010). As relatively few DHS surveys include information on Polio 0 or a second measles containing vaccination (MCV2), we are restricted to the five types (BCG, DPT 1-3, Polio 1-3, MCV1, and maternal tetanus) if we wish to use all available datasets. Our data does not distinguish between a monovalent measles vaccine and the combined measles, mumps, and rubella (MMR) vaccine, or between IPV and OPV. A summary schedule for the relevant vaccines is presented in table 1.

Table 1: World Health Organization Vaccination Schedule

Vaccine	Typical 1st Dose	Recommended Doses	Usual Interval Between Doses
BCG	At Birth	1	
DPT	6 Weeks	3	4 Weeks
Polio	Birth/6 weeks	4/3	4 Weeks
Measles	9/12 Months	1/2	4 Weeks
Maternal Tetanus	Pregnancy	Depends on Vaccination History	

Note: A more comprehensive account of when vaccines are to be administered is available from the WHO. See www.who.int/immunization/policy/Immunization_routine_table2.pdf for infants, and www.who.int/reproductivehealth/publications/maternal_perinatal_health/immunization_tetanus.pdf for maternal tetanus. See www.who.int/immunization/monitoring_surveillance/routine/coverage/en/ for WHO coverage estimates, and www.unicef.org/supply/files/MMR.pdf and <http://www.unicef.org/supply/files/TT.pdf> for cost estimates.

As DPT and Polio vaccinations are typically administered at the same time, we found it is not possible to separately identify the impact of each type, since children tend to have both or neither, making them collinear. We combine DPT and Polio into a single variable where each dose counts for 1/6. Therefore,

receiving a full schedule of DPT and Polio results in a score of 1. For the other child vaccinations (BCG and measles), we construct a binary variable for each child indicating whether they received the relevant vaccine dose. In addition, women report the number of tetanus toxoid injections received during their last pregnancy, and we use this as a child health intervention since immunity to tetanus is transferred to the child in utero (Demicheli et al., 2013). As the recommended dose varies depending on the woman’s vaccination history, we construct an indicator for whether any tetanus vaccinations were received during pregnancy. We did not find any association with a second tetanus vaccination. We have data on maternal tetanus injections only for the pregnancies in the last five years, which does not give information about injections during prior pregnancies. Even if the mother is not injected during the most recent pregnancy, she may have continuing immunity from the prior vaccinations which we will not be able to measure in our data.

A complication is that childhood vaccination information in the DHS is typically only collected for children who are alive, a common limitation of survey data, and so we cannot match child mortality to childhood vaccinations at the individual level (except for maternal tetanus vaccination, which is recorded for all women in our sample). To avoid this problem, we aggregate the data on mortality and vaccination coverage to the level of the DHS primary sampling unit (PSU) cluster. The Demographic and Health Survey in each country adopts a multistage sampling approach which involves first stratification by region, and then by urban and urban rural residence within each region (Corsi et al., 2012). Potential sampling units are defined by geographic localities, usually enumeration areas from the most recent national census. Primary sampling units, our clusters, are randomly selected from these enumeration areas within each strata. Once these primary sampling units are chosen, interviewers visit the area and sample a subset of the households in that location to identify and interview eligible respondents. When we aggregate our data to the cluster level, we are therefore calculating sample averages for localized geographic areas based on households which are in close proximity.

As we expect an association between vaccination status and mortality, the vaccination rate among the children who have died may differ from the vaccination rate among the children who survive, and ignoring the missing data could induce selection bias in our estimates of cluster vaccination rates, as well as in our estimates of the association between vaccination status and mortality (Jensen et al., 2007). Therefore, we implement a correction for this problem based on Bayes’ rule (Reniers and Eaton, 2009), and an initial estimate of the relative risk of mortality for each vaccination type which we obtain from the data.

2.2 Correcting Estimates of the Impact of Vaccination Coverage for Missing Data

The proportion of children vaccinated in a particular cluster ($p(vacc)$) is given by vaccination rate among children who have died ($p(vacc|dead)$), weighted by the proportion of children in that cluster who have died ($Dead$), plus the vaccination rate among the children who are alive ($p(vacc|alive)$), weighted by the proportion of children in that cluster who are alive ($Alive$).

$$p(vacc) = p(vacc|dead).Dead + p(vacc|alive).Alive$$

$p(vacc|dead)$ is unobserved, however by Bayes' Rule we can write this expression as a function of the relative risk of mortality for vaccination status.

$$p(vacc|dead) = \frac{p(dead|vacc).p(vacc)}{p(dead|vacc).p(vacc) + p(dead|not\ vacc).(1 - p(vacc))}$$

Dividing above and below by $p(dead|vacc)$, this equates to:

$$\frac{p(vacc)}{p(vacc) + (1 - p(vacc)).RR(dead|not\ vacc)}$$

Where $RR(dead|not\ vacc)$ is the relative risk of mortality for those who were not vaccinated, given by $\frac{p(dead|not\ vacc)}{p(dead|vacc)}$. It follows that we can derive a correction to the observed vaccination rate using this relative risk to calculate the true vaccination rate in the cluster based on the solution to the following equation:

$$p(vacc) = \frac{p(vacc)}{p(vacc) + (1 - p(vacc)).RR(died|not\ vacc)}.Dead + p(vacc|alive).Alive$$

Assuming the proportion of dead and living children, as well as the relative risk, is known, we then have a single equation with one unknown ($p(vacc)$). The proportion of surviving children ($Alive$) and the proportion of children who have died ($Dead$) in each cluster can be obtained from the data, however using the observed values in calculating the corrected vaccination rates is problematic. The proportion of children who have died, $Dead = (1 - Alive)$, is essentially the dependent variable in our regression analysis, which is what

we are trying to explain. Using the outcome directly as a component of our explanatory variable clearly opens the argument that the explanation is vacuous. More formally, the error term in our regression analysis clearly contributes to the outcome (*Dead*), and hence any explanatory variable that included the actual value of *Dead* as a component is going to be correlated with the error term, violating the assumptions required for estimation. Therefore, we replace these terms with the expected cluster mortality and survival rates ($E(Alive)$ and $E(Dead)$), which we estimate from the Poisson model described below. These terms are functions of the existing explanatory variables alone, and correct, in expectation, the bias induced by only measuring the vaccination status of living children. Then, solving for $p(vacc)$ using the standard quadratic formula, we obtain:

$$\begin{aligned}
p(vacc) = & \frac{(-E(Dead) - p(vacc|alive).E(Alive) + RR(died|not\ vacc) + p(vacc|alive).E(Alive).RR(died|not\ vacc))}{2(RR(died|not\ vacc) - 1)} \\
& \pm \\
& \left(\sqrt{(-4.p(vacc|alive).Alive.(RR(died|not\ vacc) - 1).RR(died|not\ vacc) + (E(Dead) + p(vacc|alive) \right. \\
& \quad \left. - RR(died|not\ vacc) - RR(died|not\ vacc) - p(vacc|alive).RR(died|not\ vacc)))^2} \right) \\
& \left/ 2(RR(died|not\ vacc) - 1) \right.
\end{aligned}$$

This equation will have one root in the interval 0-1 ([Reniers and Eaton, 2009](#)). We can estimate each of the quantities on the right hand side from the data, and use this formula to obtain corrected estimates of vaccination coverage for DPT/Polio, BCG, measles, and the mean vaccination rate (BCG_0 , $DPT/Polio_0$, $Measles_0$, $Vaccination\ Mean_0$) for each cluster using the following procedure. We firstly estimate the relative risk of mortality (calculated as the ratio of predicted mortality for 0% coverage relative to 100% coverage), $RR(died|not\ vacc)_0$, separately for each vaccination type using a Poisson regression model, adjusting for covariates, and the observed vaccination rates in each cluster. Then, we obtain the predicted mortality and survival rates in each cluster from this model ($E(Alive)$ and $E(Dead)$), as well as the first iteration of the corrected estimate of vaccination coverage for each vaccination type (BCG_1 , $DPT/Polio_1$, $Measles_1$, $Vaccination\ Mean_1$) in each cluster using this estimate of relative risk and the formula above.

The relative risk for vaccination type is then re-calculated using the corrected coverage rates to obtain $RR(died|not\ vacc)_1$. We iterate over this procedure 10 times to obtain a final estimate of corrected coverage (BCG_{10} , $DPT/Polio_{10}$, $Measles_{10}$, $Vaccination\ Mean_{10}$) and a final estimate of the relative risk ($RR(died|not\ vacc)_{10}$). Overall, the coverage rates are not much affected by the omission of data on children who have died, and in particular, the estimated coverage rates barely change after the first iteration, as shown in Table A3 in the appendix. In general, this will be the case unless both mortality and the relative risk of mortality from not being vaccinated is very high. We use these corrected coverage rates as our independent variables in the model presented in table 2.

2.3 Poisson Regression Model

This approach, where we aggregate at the cluster level, gives us 68,490 observations. We excluded an additional 79 clusters where the predicted mortality was 100%, as this would have result in a corrected vaccination rate of 0% for these clusters. However, we have verified that our results are not sensitive to their inclusion. Following the previous literature (Murray et al., 2003), we define the four vaccination rates in a cluster as the proportion of children surviving to 12 months who had received the relevant doses (a single dose for BCG and measles, the combined 6 doses of DPT and Polio, and whether the mother had received a tetanus shot during pregnancy), therefore clusters without any surviving children aged 12 months or greater are excluded from the analysis. We additionally estimate the average vaccination rate in a cluster as the mean of these four indicators. Figure A1 in the appendix is a histogram showing the distribution of average vaccination coverage across clusters.

We use modified Poisson regression to estimate the relative risk for the average vaccination rate using the following model (Frome and Checkoway, 1985):

$$\lambda_c = exp(\alpha + \beta \text{ Vaccination Rate}_c + X_c' \gamma + \mu_c)$$

Where λ_c is the number of children in the cluster who have died, α is a constant, $VaccinationRate_c$ is the average vaccination rate in the cluster, β is the associated parameter measuring relative risk of vaccination coverage, X_c are the independent variables measured at the cluster level, γ is the parameter vector associated with these control variables, and μ_c is an error term. X_c includes the number of births in the cluster with the coefficient offset to 1, so the number of child deaths is proportional to the number of births, and the

other explanatory variables affect the mortality rate. We included deaths of children under the age of one in our analysis (even though they may have been too young to have received all basic vaccinations) to capture potential spillover effects, however when we excluded this age group we found very similar results. The advantage of the Poisson model is that it allows us to estimate the relative risk directly. The expected mortality rates for use in our correction for missing data can then be obtained from:

$$E(\widehat{Dead})_c = \frac{\exp(\hat{\alpha} + \hat{\beta} \text{ Vaccination Rate}_c + X'_c \hat{\gamma})}{\text{Number of Births}_c}$$

Using the estimated regression parameters $(\hat{\alpha}, \hat{\beta}, \hat{\gamma})$ from our Poisson model. We also estimate the relative risk for each of the 4 vaccination types (BCG, DPT/Polio, measles, and maternal tetanus) using a model where we control for all four vaccination types simultaneously.

A potential concern with our model is that the vaccination rate is correlated with some other feature of the cluster which we do not adequately measure, such as underlying disease environment ([Fine et al., 2009](#)). If this omitted variable is correlated with vaccination coverage, our estimates of the effects of vaccination coverage could be biased. We control for this to the extent possible using measured covariates in the clusters. Table A2 in the appendix gives the full results showing these covariates.

All of our other independent variables are also aggregated to the cluster level; they include year of birth, number of siblings, gender, place of birth, birth interval, mother's age, type of place of residence (urban or rural), mother's education, flush toilet access, piped water access, mother's partner's education, mother's marital status, mother's religion, household wealth index, and whether the mother had antenatal visits for that pregnancy. We also control for months between the interview and birth as a measure of exposure risk, country-specific fixed effects and time trends.

3 Results

Table 2 presents results for vaccination coverage using the Poisson regression model described above, with cluster child mortality as the dependent variable and adjusting for other cluster characteristics. Columns 2 and 4 present results using coverage rates which are adjusted for missing data on children who have died. Using the raw coverage rate, in Column 1 of Table 2, an increase in the mean vaccination coverage is associated with a relative risk of 0.76, that is to say moving from 0% coverage to 100% coverage on all

vaccination types (BCG, DPT/Polio, measles, and maternal tetanus) is associated with a decrease in cluster level mortality of 24%. Column 2, which corrects for the selection effect of not measuring vaccination status of the dead children, implies a slightly lower relative risk of mortality of 0.73.

We also implement a model where we test whether the mix of vaccines affects mortality. This is reported in Columns 3 and 4 of Table 2. The mix of vaccination in a cluster is likely to depend on the available supply, and factors such as donor funds or campaigns initiated as part of supplementary immunization activities (SIA) (Biellik et al., 2002; Otten et al., 2005). Column 3 disaggregates the vaccination types, and column 4 does the same using the vaccination data that has been corrected for mortality selection. The results indicate that measles is associated with a relative risk of 0.83, while maternal tetanus is associated with a relative risk of 0.92. Thus, most of our estimated effect of overall vaccination on cluster mortality comes from these two vaccines, the effects of BCG, DPT and Polio vaccination appear to be very small.

Table 2: Results for Poisson Model of Cluster Vaccination Coverage and Cluster Mortality

Variables	Relative Risk Cluster Level Under 5 Mortality (95% CI)	Relative Risk Cluster Level Under 5 Mortality (95% CI)	Relative Risk Cluster Level Under 5 Mortality (95% CI)	Relative Risk Cluster Level Under 5 Mortality (95% CI)
Cluster Vaccination Average Coverage	0.76 (0.71, 0.81)	0.73 (0.68, 0.77)		
Cluster BCG Coverage			1.04 (0.96, 1.12)	1.03 (0.96, 1.11)
Cluster DPT Polio Coverage			0.97 (0.89, 1.06)	0.97 (0.89, 1.06)
Cluster Measles Coverage			0.83 (0.77, 0.89)	0.83 (0.78, 0.89)
Cluster Maternal Tetanus Coverage			0.92 (0.86, 0.97)	0.92 (0.86, 0.97)
Corrected for Missing Data on Children who Died	No	Yes	No	Yes
Country Fixed Effects and Country Time Trends	Yes	Yes	Yes	Yes
Full Set of Control Variables	Yes	Yes	Yes	Yes
Number of Clusters	68,490	68,490	68,490	68,490

Note: Demographic and Health Survey data are available from www.dhsprogram.com. All variables are averages at the level of the DHS primary sampling unit cluster, based on 149 surveys in 62 countries, and 960,271 children born between 1985 and 2011. Coefficients illustrate the relative risk of moving from 0% vaccination coverage to 100% coverage (on the mortality of children born in the 5 years prior to interview). Columns 1 and 3 are based on the raw vaccination coverage in a cluster (defined as the proportion of children one year or older who have received the relevant doses), while columns 2 and 4 adjust the vaccination data for the selection effect due to non-reporting of vaccination status of children who have died. In addition to country fixed effects, country time trends, the control variables (all cluster level averages) include year of birth, gender, place of birth, birth interval, mother's age, type of place of residence, mother's education, flush toilet access, piped water access, mother's partner's education, mother's marital status, mother's religion, household wealth index, number of siblings, and whether the mother had antenatal visits for that pregnancy. We also control for months between the interview and birth as a measure of exposure risk.

4 Discussion

Our results imply that vaccination coverage has a substantial impact on under five mortality at the cluster level, particularly for measles and maternal tetanus vaccination. These results are consistent with recent evidence on the non-specific effects of vaccines from previous observational studies, animal studies and randomized control trials (Shann, 2010). On the basis of these findings, there are therefore likely to be substantial reductions in child mortality associated with further increases in vaccination coverage, particularly additional immunization associated with measles and maternal tetanus in sub-Saharan Africa, where vaccination rates lag behind other regions (Bosch-Capblanch et al., 2012).

Our population-level estimates provide new evidence on the association between all-cause mortality and coverage of basic childhood vaccinations using nationally representative samples in diverse settings across 62 countries. Generally, it is not possible to estimate the association between vaccination status and mortality at the individual level in household survey data, such as the DHS, because the vaccination status of children who have died is not usually reported (Cutts et al., 2013). Our approach of aggregating the data and correcting for this potential selection bias allows us to estimate this relationship at the cluster level. An additional advantage of this aggregate analysis is that it allows us to capture potential herd immunity effects (John and Samuel, 2000; VanderWeele and Tchetgen, 2011; VanderWeele et al., 2012), which would not typically be observed in an individual-level analysis. Moreover, our focus on all-cause mortality avoids the issue of misreporting of cause of death in studies that use cause-specific mortality (Dabaghi et al., 2009), and allows for the possibility of non-specific effects of vaccination. There is typically substantial variation in vaccination coverage within countries and even within regions (Bosch-Capblanch et al., 2012), and conducting the analysis at these higher levels of aggregation will mask this heterogeneity and potentially attenuate estimates of the effects of interest. DHS clusters are small geographic areas, and therefore the households in each cluster are in close proximity, making this the ideal unit of analysis to investigate the full impact of vaccine coverage. Demonstrating that similar estimates are obtained from a variety of different estimation strategies in a variety of different populations strengthens the case for increasing vaccination coverage as an effective intervention to improve child health in low and middle income countries (Concato et al., 2000).

There were 7.6 million child deaths in 2010, down from 9.6 million in 2000, a reduction in the under five mortality rate from 73 to 57 (Liu et al., 2012). The annual decrease in the under five mortality rate from 1990-2010 was 2.1%, compared to the 4.4% necessary to meet the fourth Millennium Development Goal

(MDG) (Rajaratnam et al., 2010). Therefore, despite recent progress in reducing under five mortality, a renewed focus on implementing interventions which will allow countries to reach this target is likely to be required, particularly those interventions which are most cost effective and easy to implement. Measles vaccination coverage is one of the indicators for monitoring progress towards MDG 4, and further increases in immunization may provide an opportunity to aid in achieving this goal.

Results in this paper imply that the basic vaccines provide a viable means of achieving progress towards this target of reducing child mortality. From 1990 to 2010, the number of annual child deaths globally fell from 12 million to 7.6 million (Hill et al., 2012). Over the same time period, the corresponding measles vaccination global coverage rate rose from 73% to 84%, according to WHO-UNICEF estimates. The corresponding estimate from our sample indicates that 64% of children were vaccinated against measles in 1986-1990, compared to 84% in 2006-2010. We were unable to find global estimates for maternal tetanus coverage for the relevant time period, however our data indicate that 56% of children had mothers who had been vaccinated for tetanus before pregnancy in 1986-1990, as compared to 60% in 2006-2010. Using the estimates from table 2 implies that the increase in measles and tetanus coverage alone were responsible for a $0.20 \times 17 + 0.04 \times 8 = 3.7\%$ fall in global mortality. The mean vaccination rate in our data increased from 65% in 1986-1990 to 81% in 2006-2010, which corresponds to a reduction in mortality of 4.5%. Overall, coverage estimates indicate that there is substantial scope for further increasing vaccination rates (Pegurri et al., 2005), particularly in sub-Saharan Africa (Bosch-Capblanch et al., 2012).

It is reasonable to ask whether expanding coverage of measles and maternal tetanus would be cost effective strategies for reducing child mortality. If measles coverage could be raised a further 16 percentage points to 100%, this would equate to a roughly 3% reduction in mortality, or an estimated reduction of 210,000 deaths (under the figures provided in Hill et al. (2012)). For maternal tetanus, our estimates imply that increasing immunization coverage by 40 percentage points to 100% would result in approximately 240,000 fewer deaths.

According to UN estimates, the lowest cost of a single dose MMR vaccine is \$2.05, while the lowest cost for a maternal tetanus dose is \$0.05 (see the note to Table 1 for further details). Under the simplifying assumption that raising measles vaccination coverage by 16% would require an extra $133m \times 16\% = 21m$ doses, and $21m \times 2.05 = \$43.05m$ expenditure, this results in an approximate cost per life saved of $\frac{43.05m}{210,000} = \205 . Likewise, for tetanus, assuming that raising coverage by 40% would require an additional $133m \times 40\% = 53m$ doses, and $53m \times \$0.05 = \$2.7m$ expenditure, results in an approximate cost per life saved of $\frac{2.7m}{240,000} = \$11$.

While these calculations are based on highly simplified assumptions, and only account for the cost of

vaccines themselves and not administration or roll-out of expanded programs, these figures nevertheless provide some indication that increases in vaccination coverage as a means to reduce child mortality and achieve the targets laid out in the MDGs are likely to be highly cost effective, particularly for maternal tetanus immunization. For example, the estimated cost of full immunization for BCG, DPT, polio, and measles in GAVI countries was \$4 in 2011 ([Gandhi et al., 2013](#)). Moreover, estimates based solely on direct health benefits may understate the value of vaccines as there are likely to be additional benefits to society above and beyond their protective effects on mortality ([Bärnighausen et al., 2014](#); [Bloom et al., 2005](#); [Deogaonkar et al., 2012](#); [Ozawa et al., 2012](#)). For example, previous studies have linked increases in vaccination coverage to improvements in human capital ([Bloom et al., 2012](#); [Canning et al., 2011](#)).

There are important limitations associated with estimating the effects of vaccination status from household surveys ([Fine et al., 2009](#)), and future research should adopt methods for further validating the causal relationship between immunization and mortality ([Farrington et al., 2009](#); [Pollard, 2012](#); [Sachdev, 2014](#)), and further investigating the mechanisms underlying the association between vaccination and all-cause mortality ([Kleinnijenhuis et al., 2012](#); [Ritz et al., 2013](#)). Our results are somewhat smaller than the limited available evidence on non-specific effects of vaccines from RCTs ([Shann, 2013](#)), however this is likely to reflect a number of drawbacks to the data. First, we estimate cluster level vaccination coverage from the survey, which could introduce measurement error and attenuation bias. In addition, we rely on maternal reports of vaccination status when vaccination cards are not available, which could also induce measurement error. We use a binary indicator for BCG, measles and maternal tetanus, and assign the value one to receiving 3 doses of Polio and 3 doses of DPT. However, there are many potential ways to measure vaccination coverage. Second, we do not consider the timing or ordering of vaccination, which is also likely to have an impact on child outcomes ([Aaby et al., 2015](#); [Clark and Sanderson, 2009](#)). We did not find any adverse impact of the DPT vaccine, however we were unable to estimate its relative risk separately from that of Polio. Third, we do not examine potential interactions or non-linearities in the data. Vaccine efficacy may vary with country, cluster, family, and child level characteristics ([Bishai et al., 2003](#)). The literature has documented potential effect modification by sex and receipt of vitamin A supplementation ([Aaby et al., 2004b](#); [Benn et al., 2014](#)). Investigating these interactions is an important direction for future research. Finally, our estimates come from data which are not globally representative, only nationally representative. While we use all available Demographic and Health Surveys from round 2 on, countries are not sampled randomly, and therefore any direct comparison between rates estimated in the data and global estimates should be made with this limitation in mind.

References

- P. Aaby, J. Bukh, I. M. Lisse, and A. J. Smits. Measles vaccination and reduction in child mortality: a community study from Guinea-Bissau. *Journal of Infection*, 8(1):13–21, 1984.
- P. Aaby, B. Samb, F. Simondon, A. M. C. Seck, K. Knudsen, and H. Whittle. Non-specific beneficial effect of measles immunisation: analysis of mortality studies from developing countries. *BMJ*, 311(7003):481–485, 1995.
- P. Aaby, A. Bhuiya, L. Nahar, K. Knudsen, A. De Francisco, and M. Strong. The survival benefit of measles immunization may not be explained entirely by the prevention of measles disease: a community study from rural Bangladesh. *International Journal of Epidemiology*, 32(1):106–115, 2003.
- P. Aaby, H. Jensen, J. Gomes, M. Fernandes, and I. M. Lisse. The introduction of diphtheria-tetanus-pertussis vaccine and child mortality in rural Guinea-Bissau: an observational study. *International Journal of Epidemiology*, 33(2):374–380, 2004a.
- P. Aaby, H. Jensen, A. Rodrigues, M.-L. Garly, C. S. Benn, I. M. Lisse, and F. Simondon. Divergent female-male mortality ratios associated with different routine vaccinations among female-male twin pairs. *International Journal of Epidemiology*, 33(2):367–373, 2004b.
- P. Aaby, C. Martins, M.-L. Garly, C. Bal, A. Andersen, A. Rodrigues, H. Ravn, I. M. Lisse, C. S. Benn, and H. Whittle. Non-specific effects of standard measles vaccine at 4.5 and 9 months of age on childhood mortality: randomised controlled trial. *BMJ*, 341:c6495, 2010.
- P. Aaby, C. Benn, J. Nielsen, I. M. Lisse, A. Rodrigues, and H. Ravn. Testing the hypothesis that diphtheria-tetanus-pertussis vaccine has negative non-specific and sex-differential effects on child survival in high-mortality countries. *BMJ Open*, 2(3):e000707, 2012.
- P. Aaby, C. L. Martins, H. Ravn, A. Rodrigues, H. C. Whittle, and C. S. Benn. Is early measles vaccination better than later measles vaccination? *Transactions of The Royal Society of Tropical Medicine and Hygiene*, 109(1):16–28, 2015.
- T. Bärnighausen, D. E. Bloom, E. T. Cafiero-Fonseca, and J. C. O'Brien. Valuing vaccination. *Proceedings of the National Academy of Sciences*, 111(34):12313–12319, Aug. 2014.

- C. S. Benn, C. L. Martins, A. B. Fisker, B. R. Diness, M.-L. Garly, I. Balde, A. Rodrigues, H. Whittle, and P. Aaby. Interaction between neonatal vitamin A supplementation and timing of measles vaccination: a retrospective analysis of three randomized trials from Guinea-Bissau. *Vaccine*, 32(42):5468–5474, 2014.
- R. Biellik, S. Madema, A. Taole, A. Kutsulukuta, E. Allies, R. Eggers, N. Ngcobo, M. Nxumalo, A. Shearley, and E. Mabuzane. First 5 years of measles elimination in southern Africa: 1996-2000. *The Lancet*, 359(9317):1564–1568, 2002.
- D. Bishai, M. Koenig, and M. A. Khan. Measles vaccination improves the equity of health outcomes: evidence from Bangladesh. *Health Economics*, 12(5):415–419, 2003.
- D. Bishai, B. Johns, D. Nair, J. Nabyonga-Orem, B. Fiona-Makmot, E. Simons, and A. Dabbagh. The cost-effectiveness of supplementary immunization activities for measles: a stochastic model for Uganda. *Journal of Infectious Diseases*, 204(suppl 1):S107–S115, 2011.
- R. E. Black, S. Cousens, H. L. Johnson, J. E. Lawn, I. Rudan, D. G. Bassani, P. Jha, H. Campbell, C. F. Walker, and R. Cibulskis. Global, regional, and national causes of child mortality in 2008: a systematic analysis. *The Lancet*, 375(9730):1969–1987, 2010.
- D. E. Bloom, D. Canning, and M. Weston. The value of vaccination. *World Economics*, 6(3):15, 2005.
- D. E. Bloom, D. Canning, and E. S. Shenoy. The effect of vaccination on children’s physical and cognitive development in the Philippines. *Applied Economics*, 44(21):2777–2783, 2012.
- X. Bosch-Capblanch, K. Banerjee, and A. Burton. Unvaccinated children in years of increasing coverage: how many and who are they? Evidence from 96 low-and middle-income countries. *Tropical Medicine & International Health*, 17(6):697–710, 2012.
- L. Brenzel, L. J. Wolfson, J. Fox-Rushby, M. Miller, and N. A. Halsey. Vaccine-preventable diseases. In *Disease control priorities in developing countries, 2nd Edition*, volume 2, pages 389–412. World Bank, Washington DC, 2006.
- J. Bryce, C. Boschi-Pinto, K. Shibuya, and R. E. Black. WHO estimates of the causes of death in children. *The Lancet*, 365(9465):1147–1152, 2005.
- A. Burton, R. Monasch, B. Lautenbach, M. Gacic-Dobo, M. Neill, R. Karimov, L. Wolfson, G. Jones, and M. Birmingham. WHO and UNICEF estimates of national infant immunization coverage: methods and processes. *Bulletin of the World Health Organization*, 87(7):535–541, 2009.

- D. Canning, A. Razzaque, J. Driessen, D. G. Walker, P. K. Streatfield, and M. Yunus. The effect of maternal tetanus immunization on childrens' schooling attainment in Matlab, Bangladesh: follow-up of a randomized trial. *Social Science & Medicine*, 72(9):1429–1436, 2011.
- A. Clark and C. Sanderson. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. *The Lancet*, 373(9674):1543–1549, 2009.
- J. D. Clemens, B. F. Stanton, J. Chakraborty, S. Chowdhury, M. R. Rao, A. Mohammed, S. Zimicki, and B. Wojtyniak. Measles vaccination and childhood mortality in rural Bangladesh. *American Journal of Epidemiology*, 128(6):1330–1339, 1988.
- G. A. Colditz, T. F. Brewer, C. S. Berkey, M. E. Wilson, E. Burdick, H. V. Fineberg, and F. Mosteller. Efficacy of BCG vaccine in the prevention of tuberculosis: meta-analysis of the published literature. *JAMA*, 271(9):698–702, 1994.
- J. Concato, N. Shah, and R. I. Horwitz. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *New England Journal of Medicine*, 342(25):1887–1892, 2000.
- D. J. Corsi, M. Neuman, J. E. Finlay, and S. Subramanian. Demographic and Health Surveys: a profile. *International Journal of Epidemiology*, 41(6):1602–1613, 2012.
- F. T. Cutts, H. S. Izurieta, and D. A. Rhoda. Measuring coverage in MNCH: Design, implementation, and interpretation challenges associated with tracking vaccination coverage using household surveys. *PLoS Medicine*, 10(5):e1001404, 2013.
- A. Dabbagh, M. Gacic-Dobo, E. Simons, D. Featherstone, P. Strebel, J. Okwo-Bele, E. Hoekstra, M. Chopra, A. Uzicanin, and S. Cochi. Global measles mortality, 2000-2008. *Morbidity and Mortality Weekly Report*, 58(47):1321–1326, 2009.
- V. Demicheli, A. Barale, and A. Rivetti. Vaccines for women to prevent neonatal tetanus. *Cochrane Database of Systematic Reviews*, 5:CD002959, 2013.
- R. Deogaonkar, R. Hutubessy, I. van der Putten, S. Evers, and M. Jit. Systematic review of studies evaluating the broader economic impact of vaccination in low and middle income countries. *BMC Public Health*, 12(1):878, 2012.
- M. S. Fabric, Y. Choi, and S. Bird. A systematic review of Demographic and Health Surveys: data availability and utilization for research. *Bulletin of the World Health Organization*, 90(8):604–612, 2012.

- C. Farrington, M. Firth, L. Moulton, H. Ravn, P. Andersen, and S. Evans. Epidemiological studies of the non-specific effects of vaccines: II - methodological issues in the design and analysis of cohort studies. *Tropical Medicine & International Health*, 14(9):977–985, 2009.
- D. R. Feikin, B. Flannery, M. J. Hamel, M. Stack, and P. Hansen. Vaccine preventable diseases in children. In *Disease control priorities in developing countries, 3rd Edition*, volume 2: Reproductive, Maternal, Newborn and Child Health. Centers for Disease Control and Prevention, Atlanta, GA, USA, 2015.
- P. E. Fine, T. N. Williams, P. Aaby, K. Källander, L. H. Moulton, K. L. Flanagan, P. G. Smith, and C. S. Benn. Epidemiological studies of the “non-specific effects” of vaccines: I-data collection in observational studies. *Tropical Medicine & International Health*, 14(9):969–976, 2009.
- G. Fink, I. Günther, and K. Hill. The effect of water and sanitation on child health: evidence from the Demographic and Health Surveys 1986-2007. *International Journal of Epidemiology*, 40(5):1196–1204, 2011.
- E. L. Frome and H. Checkoway. Use of Poisson regression models in estimating incidence rates and ratios. *American Journal of Epidemiology*, 121(2):309–323, 1985.
- G. Gandhi, P. Lydon, S. Cornejo, L. Brenzel, S. Wrobel, and H. Chang. Projections of costs, financing, and additional resource requirements for low-and lower middle-income country immunization programs over the decade, 2011-2020. *Vaccine*, 31:B137–B148, 2013.
- J. D. Goldhaber-Fiebert, M. Lipsitch, A. Mahal, A. M. Zaslavsky, and J. A. Salomon. Quantifying child mortality reductions related to measles vaccination. *PloS ONE*, 5(11):e13842, 2010.
- A. Hancioglu and F. Arnold. Measuring coverage in MNCH: Tracking progress in health for women and children using DHS and MICS household surveys. *PLoS Medicine*, 10(5):e1001391, 2013.
- J. B. Harris, M. Gacic-Dobo, R. Eggers, D. W. Brown, and S. V. Sodha. Global routine vaccination coverage, 2013. *Morbidity and Mortality Weekly Report*, 63(46):1055–1058, 2014.
- K. Hill, D. You, M. Inoue, and M. Z. Oestergaard. Child mortality estimation: accelerated progress in reducing global child mortality, 1990-2010. *PLoS Medicine*, 9(8):e1001303, 2012.
- E. A. Holt, R. Boulos, N. A. Halsey, L.-M. Boulos, and C. Boulos. Childhood survival in Haiti: protective effect of measles vaccination. *Pediatrics*, 85(2):188–194, 1990.

- H. Jensen, C. S. Benn, I. M. Lisse, A. Rodrigues, P. K. Andersen, and P. Aaby. Survival bias in observational studies of the impact of routine immunizations on childhood survival. *Tropical Medicine & International Health*, 12(1):5–14, 2007.
- T. J. John and R. Samuel. Herd immunity and herd effect: new insights and definitions. *European Journal of Epidemiology*, 16(7):601–606, 2000.
- J. Kleinnijenhuis, J. Quintin, F. Preijers, L. A. Joosten, D. C. Ifrim, S. Saeed, C. Jacobs, J. van Loenhout, D. de Jong, and H. G. Stunnenberg. Bacille Calmette-Guérin induces NOD2-dependent non-specific protection from reinfection via epigenetic reprogramming of monocytes. *Proceedings of the National Academy of Sciences*, 109(43):17537–17542, 2012.
- M. A. Koenig, N. C. Roy, T. McElrath, M. Shahidullah, and B. Wojtyniak. Duration of protective immunity conferred by maternal tetanus toxoid immunization: further evidence from Matlab, Bangladesh. *American Journal of Public Health*, 88(6):903–907, 1998.
- M. A. Koenig, D. Bishai, and M. A. Khan. Health interventions and health equity: the example of measles vaccination in Bangladesh. *Population and Development Review*, 27(2):283–302, 2001.
- R. Langsten and K. Hill. The accuracy of mothers’ reports of child vaccination: evidence from rural Egypt. *Social Science & Medicine*, 46(9):1205–1212, 1998.
- L. Liu, H. L. Johnson, S. Cousens, J. Perin, S. Scott, J. E. Lawn, I. Rudan, H. Campbell, R. Cibulskis, and M. Li. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *The Lancet*, 379(9832):2151–2161, 2012.
- C. J. Murray, B. Shengelia, N. Gupta, S. Moussavi, A. Tandon, and M. Thieren. Validity of reported vaccination coverage in 45 countries. *The Lancet*, 362(9389):1022–1027, 2003.
- M. Otten, R. Kezaala, A. Fall, B. Masresha, R. Martin, L. Cairns, R. Eggers, R. Biellik, M. Grabowsky, and P. Strebel. Public-health impact of accelerated measles control in the WHO African Region 2000-03. *The Lancet*, 366(9488):832–839, 2005.
- S. Ozawa, A. Mirelman, M. L. Stack, D. G. Walker, and O. S. Levine. Cost-effectiveness and economic benefits of vaccines in low-and middle-income countries: a systematic review. *Vaccine*, 31(1):96–108, 2012.

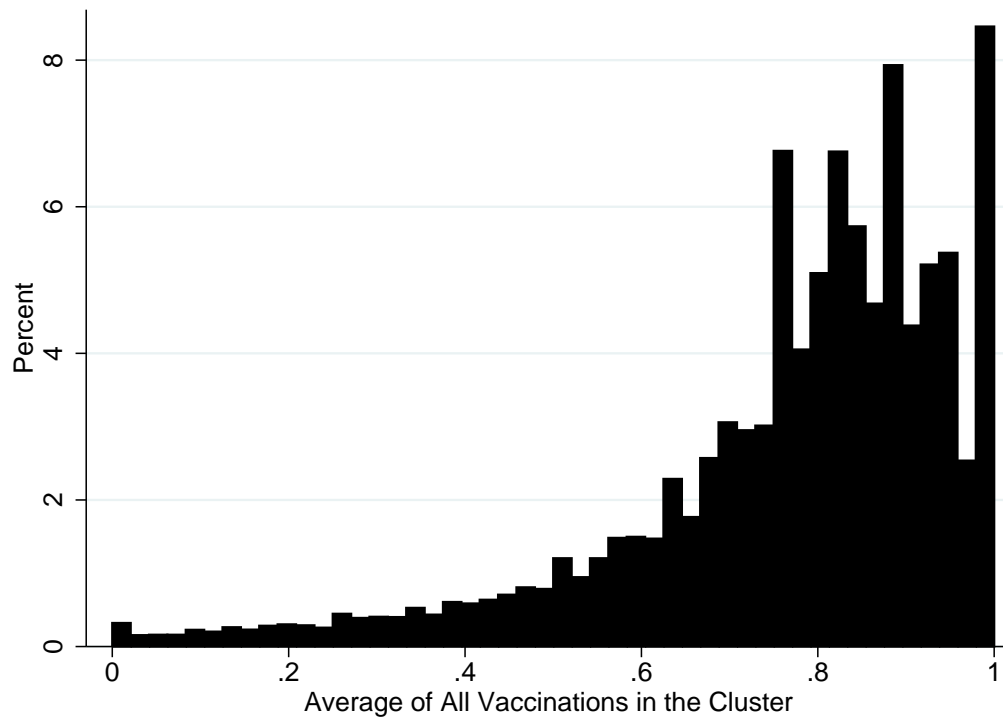
- E. Pegurri, J. A. Fox-Rushby, and W. Damian. The effects and costs of expanding the coverage of immunisation services in developing countries: a systematic literature review. *Vaccine*, 23(13):1624–1635, 2005.
- A. J. Pollard. Non-specific effects of vaccines: RCTs, not observational studies, are needed. *Archives of Disease in Childhood*, 97(8):677–8, 2012.
- J. K. Rajaratnam, J. R. Marcus, A. D. Flaxman, H. Wang, A. Levin-Rector, L. Dwyer, M. Costa, A. D. Lopez, and C. J. Murray. Neonatal, postneonatal, childhood, and under-5 mortality for 187 countries, 1970-2010: a systematic analysis of progress towards Millennium Development Goal 4. *The Lancet*, 375(9730):1988–2008, 2010.
- G. Reniers and J. Eaton. Refusal bias in hiv prevalence estimates from nationally representative seroprevalence surveys. *AIDS*, 23(5):621, 2009.
- N. Ritz, M. Mui, A. Balloch, and N. Curtis. Non-specific effect of Bacille Calmette-Guérin vaccine on the immune response to routine immunisations. *Vaccine*, 31(30):3098–3103, 2013.
- H. S. Sachdev. Commentary: Potential implications of non-specific effects of childhood vaccines. *International Journal of Epidemiology*, 43(3):653–654, 2014.
- F. Shann. The non-specific effects of vaccines. *Archives of Disease in Childhood*, 95(9):662–667, 2010.
- F. Shann. Non-specific effects of vaccines and the reduction of mortality in children. *Clinical Therapeutics*, 35(2):109–114, 2013.
- M. L. Stack, S. Ozawa, D. M. Bishai, A. Mirelman, Y. Tam, L. Niessen, D. G. Walker, and O. S. Levine. Estimated economic benefits during the “decade of vaccines” include treatment savings, gains in labor productivity. *Health Affairs*, 30(6):1021–1028, 2011.
- A. Uzicanin and L. Zimmerman. Field effectiveness of live attenuated measles-containing vaccines: a review of published literature. *Journal of Infectious Diseases*, 204(suppl 1):S133–S149, 2011.
- M. M. Van Den Ent, D. W. Brown, E. J. Hoekstra, A. Christie, and S. L. Cochi. Measles mortality reduction contributes substantially to reduction of all cause mortality among children less than five years of age, 1990-2008. *Journal of Infectious Diseases*, 204(suppl 1):S18–S23, 2011.

- T. J. VanderWeele and E. J. T. Tchetgen. Bounding the infectiousness effect in vaccine trials. *Epidemiology*, 22(5):686, 2011.
- T. J. VanderWeele, E. J. T. Tchetgen, and M. E. Halloran. Components of the indirect effect in vaccine trials: identification of contagion and infectiousness effects. *Epidemiology*, 23(5):751, 2012.
- S. Verguet, W. Jassat, M. Y. Bertram, S. M. Tollman, C. J. Murray, D. T. Jamison, and K. J. Hofman. Supplementary immunization activities (SIAs) in South Africa: comprehensive economic evaluation of an integrated child health delivery platform. *Global Health Action*, 6, 2013.
- World Health Organization. Measles vaccines: WHO position paper. *Weekly Epidemiological Record*, 84(35): 349–360, 2009.
- World Health Organization. Polio vaccines and polio immunization in the pre-eradication era: WHO position paper. *Weekly Epidemiological Record*, 85(23):213–28, 2010.

Appendix

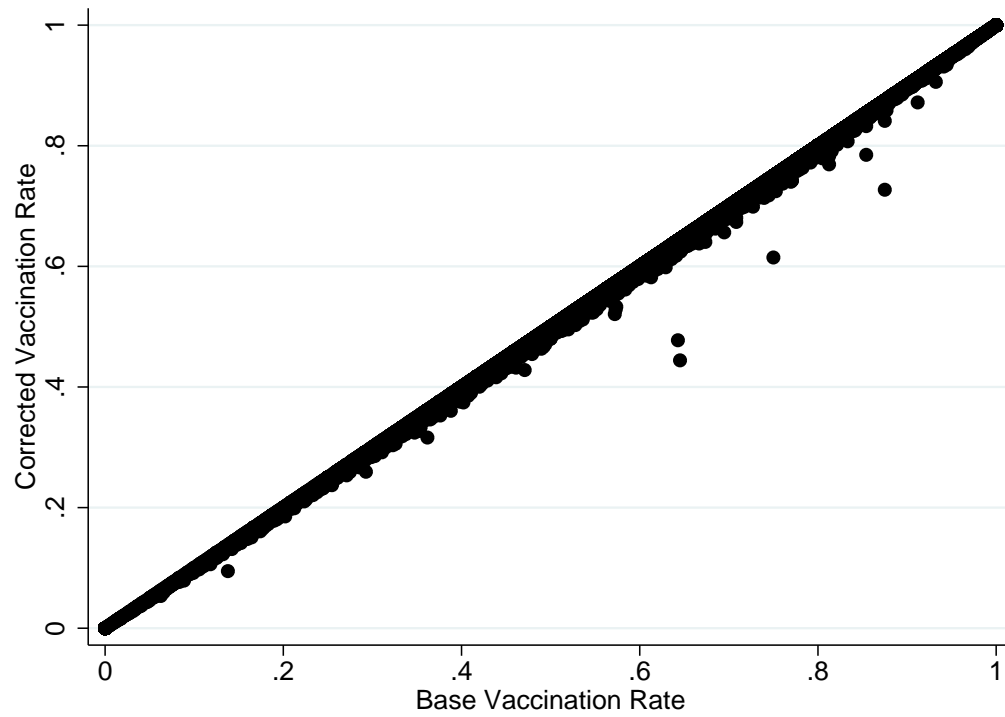
Additional Figures and Tables

Figure A1: Histogram of Mean Vaccination Coverage



Source: Demographic and Health Surveys. For BCG, measles, and maternal tetanus, we construct a binary indicator variable for each child indicating whether they received the relevant vaccine dose. We combine DPT and Polio into a single variable where each dose counts for 1/6. Therefore, receiving a full schedule of DPT and Polio results in a score of 1. Mean vaccination coverage is defined as the average of the BCG, DPT/Polio, measles, and maternal tetanus vaccination rates in the cluster. The data include 68,490 DHS primary sampling unit clusters, based on 149 surveys in 62 countries, and 960,271 children born between 1985 and 2011.

Figure A2: Scatterplot of Raw Mean Vaccination Coverage and Mortality Corrected Mean Vaccination Coverage



Source: Demographic and Health Surveys. The data include 68,490 DHS primary sampling unit clusters, based on 149 surveys in 62 countries, and 960,271 children born between 1985 and 2011. The corrected vaccination rate adjusts for missing immunization information on children who have died using the procedure described in the main text.

Table A1: Results for Cluster Vaccination Coverage and Cluster Mortality (Unadjusted for Covariates other than Country Fixed Effects and Time Trends)

Variables	Relative Risk Cluster Level Under 5 Mortality (95% CI)	Relative Risk Cluster Level Under 5 Mortality (95% CI)	Relative Risk Cluster Level Under 5 Mortality (95% CI)	Relative Risk Cluster Level Under 5 Mortality (95% CI)
Cluster Vaccination Average Coverage	0.38 (0.36 - 0.40)	0.37 (0.35 - 0.38)		
Cluster BCG Coverage			1.06 (0.98 - 1.14)	1.06 (0.98 - 1.15)
Cluster DPT Polio Coverage			0.85 (0.77 - 0.93)	0.86 (0.79 - 0.94)
Cluster Measles Coverage			0.71 (0.66 - 0.77)	0.70 (0.65 - 0.75)
Cluster Maternal Tetanus Coverage			0.57 (0.53 - 0.58)	0.56 (0.53 - 0.58)
Corrected for Missing Data on Children who Died	No	Yes	No	Yes
Country Fixed Effects and Country Time Trends	Yes	Yes	Yes	Yes
Full Set of Control Variables	No	No	No	No
Observations	68,490	68,490	68,490	68,490

Note: Demographic and Health Survey data are available from www.dhsprogram.com. All variables are averages at the level of the DHS primary sampling unit cluster, based on 149 surveys in 62 countries, and 960,271 children born between 1985 and 2011. Coefficients illustrate the relative risk of moving from 0% vaccination coverage to 100% coverage (on the mortality of children born in the 5 years prior to interview). Columns 1 and 3 are based on the raw vaccination coverage in a cluster (defined as the proportion of children one year or older who have received the relevant doses), while columns 2 and 4 adjust the vaccination data for the selection effect due to non-reporting of vaccination status of children who have died. Models control for country fixed effects and country time trends.

Table A2: Full Results for Cluster Vaccination Coverage and Cluster Mortality

Variables	Relative Risk	Relative Risk	Relative Risk	Relative Risk
	Cluster Level	Cluster Level	Cluster Level	Cluster Level
	Under 5 Mortality	Under 5 Mortality	Under 5 Mortality	Under 5 Mortality
	(95% CI)	(95% CI)	(95% CI)	(95% CI)
Cluster Vaccination Average Coverage	0.76 (0.71 - 0.81)	0.73 (0.68 - 0.77)		
Cluster BCG Coverage			1.04 (0.96 - 1.12)	1.03 (0.96 - 1.11)
Cluster DPT Polio Coverage			0.97 (0.89 - 1.06)	0.97 (0.89 - 1.06)
Cluster Measles Coverage			0.83 (0.77 - 0.89)	0.83 (0.78 - 0.89)
Cluster Maternal Tetanus Coverage			0.92 (0.86 - 0.97)	0.92 (0.86 - 0.97)
Wealth Index: Omitted=Highest				
Cluster Mean Lowest Quintile	1.12 (1.05 - 1.19)	1.11 (1.04 - 1.19)	1.12 (1.05 - 1.19)	1.12 (1.05 - 1.19)
Cluster Mean Second Quintile	1.12 (1.06 - 1.20)	1.12 (1.05 - 1.19)	1.12 (1.06 - 1.20)	1.12 (1.06 - 1.20)
Cluster Mean Third Quintile	1.06 (1.00 - 1.13)	1.06 (1.00 - 1.12)	1.06 (1.00 - 1.13)	1.06 (1.00 - 1.13)
Cluster Mean Fourth Quintile	1.08 (1.02 - 1.15)	1.08 (1.02 - 1.14)	1.08 (1.02 - 1.14)	1.08 (1.02 - 1.14)
Cluster Mean Year of Birth	0.14 (0.13 - 0.16)	0.14 (0.13 - 0.16)	0.14 (0.13 - 0.16)	0.14 (0.13 - 0.16)
Cluster Mean Sex of Child – Female	0.93 (0.90 - 0.95)	0.93 (0.90 - 0.95)	0.92 (0.90 - 0.95)	0.92 (0.90 - 0.95)
Cluster Mean Was not Multiple Birth	0.90 (0.85 - 0.96)	0.90 (0.85 - 0.96)	0.90 (0.85 - 0.96)	0.90 (0.85 - 0.96)
Place of Birth: Omitted= Own Home				
Cluster Mean Other Home	1.01 (0.93 - 1.11)	1.01 (0.93 - 1.11)	1.01 (0.92 - 1.11)	1.01 (0.92 - 1.11)
Cluster Mean Government Hospital	0.82 (0.78 - 0.87)	0.83 (0.78 - 0.87)	0.83 (0.78 - 0.88)	0.83 (0.78 - 0.88)
Cluster Mean Government Health Center	0.87 (0.82 - 0.91)	0.87 (0.83 - 0.92)	0.87 (0.82 - 0.92)	0.87 (0.82 - 0.92)
Cluster Mean Private Hospital or Clinic	0.80 (0.75 - 0.86)	0.80 (0.75 - 0.86)	0.80 (0.74 - 0.86)	0.80 (0.74 - 0.86)
Cluster Mean Other and Unknown	1.97 (1.68 - 2.31)	1.96 (1.67 - 2.30)	1.99 (1.69 - 2.33)	1.98 (1.69 - 2.32)
Birth Interval: Omitted=12-17 Months				
Cluster Mean Birth Interval First Birth	0.14 (0.12 - 0.17)	0.14 (0.12 - 0.17)	0.14 (0.12 - 0.17)	0.14 (0.12 - 0.17)
Cluster Mean Birth Interval 1-11	5.15 (3.79 - 7.00)	5.09 (3.75 - 6.92)	5.15 (3.79 - 7.00)	5.15 (3.79 - 7.00)
Cluster Mean Birth Interval 18-23	0.22 (0.19 - 0.26)	0.22 (0.19 - 0.26)	0.22 (0.19 - 0.26)	0.22 (0.19 - 0.26)
Cluster Mean Birth Interval 24+	0.12 (0.11 - 0.14)	0.12 (0.11 - 0.14)	0.12 (0.11 - 0.14)	0.12 (0.11 - 0.14)
Cluster Mean Number of Siblings	1.07 (1.06 - 1.09)	1.07 (1.05 - 1.09)	1.07 (1.05 - 1.09)	1.07 (1.05 - 1.09)
Mother's Age: Omitted=15-19				
Cluster Mean Mother's Age 20-24	0.77 (0.68 - 0.86)	0.77 (0.68 - 0.86)	0.77 (0.69 - 0.87)	0.77 (0.69 - 0.87)
Cluster Mean Mother's Age 25-29	0.63 (0.56 - 0.71)	0.63 (0.56 - 0.72)	0.64 (0.56 - 0.72)	0.63 (0.56 - 0.72)
Cluster Mean Mother's Age 30-34	0.59 (0.52 - 0.67)	0.59 (0.52 - 0.67)	0.59 (0.52 - 0.68)	0.59 (0.52 - 0.68)
Cluster Mean Mother's Age 35-39	0.59 (0.51 - 0.68)	0.59 (0.51 - 0.68)	0.59 (0.51 - 0.68)	0.59 (0.51 - 0.68)
Cluster Mean Mother's Age 40-44	0.61 (0.52 - 0.72)	0.61 (0.52 - 0.73)	0.62 (0.52 - 0.73)	0.62 (0.52 - 0.73)
Cluster Mean Mother's Age 45-49	0.70 (0.55 - 0.89)	0.70 (0.55 - 0.89)	0.70 (0.55 - 0.89)	0.70 (0.55 - 0.89)
Cluster Mean Rural Place of Residence	0.95 (0.93 - 0.98)	0.95 (0.93 - 0.98)	0.95 (0.93 - 0.98)	0.95 (0.93 - 0.98)
Mother's Highest Education: Omitted=None				
Cluster Mean Primary	0.97 (0.92 - 1.03)	0.97 (0.92 - 1.03)	0.97 (0.92 - 1.03)	0.97 (0.92 - 1.03)
Cluster Mean Secondary	0.84 (0.78 - 0.90)	0.84 (0.78 - 0.90)	0.84 (0.78 - 0.90)	0.84 (0.78 - 0.90)
Cluster Mean Higher Education	0.71 (0.60 - 0.82)	0.71 (0.61 - 0.82)	0.71 (0.60 - 0.82)	0.71 (0.60 - 0.82)
Cluster Mean Missing	0.49 (0.11 - 2.06)	0.48 (0.11 - 2.05)	0.48 (0.11 - 2.05)	0.49 (0.11 - 2.06)
Cluster Mean Flush Toilet Access	0.90 (0.86 - 0.95)	0.90 (0.86 - 0.95)	0.90 (0.86 - 0.95)	0.90 (0.86 - 0.95)
Cluster Mean Piped Water in House	0.98 (0.95 - 1.01)	0.98 (0.95 - 1.01)	0.98 (0.95 - 1.01)	0.98 (0.95 - 1.01)
Partner Education: Omitted=None				
Cluster Mean Primary	1.10 (1.03 - 1.17)	1.10 (1.03 - 1.17)	1.09 (1.03 - 1.16)	1.09 (1.03 - 1.16)
Cluster Mean Secondary	0.99 (0.92 - 1.06)	0.99 (0.92 - 1.06)	0.98 (0.92 - 1.05)	0.98 (0.92 - 1.05)

Table A2 – Continued on the Next Page

Variables	Relative Risk	Relative Risk	Relative Risk	Relative Risk
	Cluster Level	Cluster Level	Cluster Level	Cluster Level
	Under 5 Mortality (95% CI)	Under 5 Mortality (95% CI)	Under 5 Mortality (95% CI)	Under 5 Mortality (95% CI)
Cluster Mean Higher Education	0.91 (0.80 - 1.02)	0.91 (0.80 - 1.02)	0.91 (0.80 - 1.02)	0.91 (0.80 - 1.02)
Cluster Mean Missing	1.12 (1.00 - 1.25)	1.12 (1.00 - 1.25)	1.12 (1.00 - 1.25)	1.11 (1.00 - 1.24)
Marital Status: Omitted=Married				
Cluster Mean Never Married	1.11 (0.93 - 1.31)	1.11 (0.93 - 1.31)	1.11 (0.94 - 1.31)	1.11 (0.94 - 1.32)
Cluster Mean Living Together	1.11 (1.04 - 1.17)	1.11 (1.04 - 1.17)	1.10 (1.04 - 1.17)	1.10 (1.04 - 1.17)
Cluster Mean Widowed	1.80 (1.44 - 2.24)	1.79 (1.44 - 2.23)	1.79 (1.43 - 2.23)	1.79 (1.43 - 2.23)
Cluster Mean Divorced	1.90 (1.57 - 2.31)	1.90 (1.57 - 2.31)	1.90 (1.56 - 2.30)	1.90 (1.56 - 2.30)
Cluster Mean Not Living Together	1.67 (1.47 - 1.90)	1.67 (1.47 - 1.90)	1.67 (1.47 - 1.90)	1.67 (1.47 - 1.90)
Religion: Omitted=Christian				
Cluster Mean Religion Muslim	1.01 (0.97 - 1.05)	1.01 (0.97 - 1.05)	1.01 (0.97 - 1.05)	1.01 (0.97 - 1.05)
Cluster Mean Religion Jewish	0.85 (0.64 - 1.15)	0.86 (0.64 - 1.15)	0.85 (0.64 - 1.15)	0.85 (0.64 - 1.15)
Cluster Mean Religion Buddhist	0.86 (0.73 - 1.01)	0.86 (0.73 - 1.01)	0.86 (0.73 - 1.00)	0.86 (0.73 - 1.00)
Cluster Mean Religion Hindu	1.40 (1.30 - 1.51)	1.40 (1.30 - 1.51)	1.40 (1.30 - 1.51)	1.40 (1.30 - 1.51)
Cluster Mean Religion Sikh	1.13 (0.86 - 1.50)	1.14 (0.86 - 1.51)	1.15 (0.87 - 1.52)	1.15 (0.87 - 1.52)
Cluster Mean Religion Traditional	1.05 (0.95 - 1.16)	1.04 (0.95 - 1.15)	1.04 (0.95 - 1.15)	1.04 (0.95 - 1.15)
Cluster Mean Religion Other	1.07 (0.98 - 1.18)	1.07 (0.98 - 1.17)	1.08 (0.98 - 1.18)	1.08 (0.98 - 1.18)
Cluster Mean Religion None	0.87 (0.78 - 0.97)	0.87 (0.78 - 0.96)	0.86 (0.78 - 0.96)	0.87 (0.78 - 0.96)
Cluster Mean Unknown/Missing	1.07 (1.02 - 1.14)	1.08 (1.02 - 1.14)	1.07 (1.01 - 1.13)	1.07 (1.01 - 1.13)
Cluster Mean Months Since Birth	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)
Had Ante-Natal Visit: Omitted=No Visit				
Cluster Mean Had Ante-Natal Visit	0.86 (0.81 - 0.91)	0.87 (0.82 - 0.93)	0.85 (0.80 - 0.91)	0.85 (0.80 - 0.91)
Cluster Mean Ante-Natal Visit Missing	1.32 (1.21 - 1.45)	1.32 (1.21 - 1.45)	1.29 (1.18 - 1.42)	1.29 (1.18 - 1.42)
Corrected for Missing Data on Children who Died	No	Yes	No	Yes
Country Fixed Effects and Country Time Trends	Yes	Yes	Yes	Yes
Number of clusters	68,490	68,490	68,490	68,490

Note: Demographic and Health Survey data are available from www.dhsprogram.com. All variables are averages at the level of the DHS primary sampling unit cluster, based on 149 surveys in 62 countries, and 960,271 children born between 1985 and 2011. Coefficients illustrate the relative risk of moving from 0% vaccination coverage to 100% coverage (on the mortality of children born in the 5 years prior to interview). Columns 1 and 3 are based on the raw vaccination coverage in a cluster (defined as the proportion of children one year or older who have received the relevant doses), while columns 2 and 4 adjust the vaccination data for the selection effect due to non-reporting of vaccination status of children who have died.

Table A3: Corrected Cluster Vaccination Coverage Rates

Cluster Vaccination Coverage	Median	Mean	SD	N
Measles				
Base	88.89%	79.77%	25.65%	68,490
Iteration 1	88.83%	79.64%	25.75%	68,490
Iteration 2	88.83%	79.64%	25.75%	68,490
Iteration 3	88.83%	79.64%	25.75%	68,490
Iteration 4	88.83%	79.64%	25.75%	68,490
Iteration 5	88.83%	79.64%	25.75%	68,490
Iteration 6	88.83%	79.64%	25.75%	68,490
Iteration 7	88.83%	79.64%	25.75%	68,490
Iteration 8	88.83%	79.64%	25.75%	68,490
Iteration 9	88.83%	79.64%	25.75%	68,490
Iteration 10	88.83%	79.64%	25.75%	68,490
DPT Polio				
Base	88.89%	81.92%	21.22%	68,490
Iteration 1	88.89%	81.91%	21.23%	68,490
Iteration 2	88.89%	81.91%	21.23%	68,490
Iteration 3	88.89%	81.91%	21.23%	68,490
Iteration 4	88.89%	81.91%	21.23%	68,490
Iteration 5	88.89%	81.91%	21.23%	68,490
Iteration 6	88.89%	81.91%	21.23%	68,490
Iteration 7	88.89%	81.91%	21.23%	68,490
Iteration 8	88.89%	81.91%	21.23%	68,490
Iteration 9	88.89%	81.91%	21.23%	68,490
Iteration 10	88.89%	81.91%	21.23%	68,490

Table A3 – Continued on the Next Page

Cluster Vaccination Coverage	Median	Mean	SD	N
BCG				
Base	100.00%	87.28%	22.22%	68,490
Iteration 1	100.00%	87.30%	22.20%	68,490
Iteration 2	100.00%	87.29%	22.21%	68,490
Iteration 3	100.00%	87.29%	22.21%	68,490
Iteration 4	100.00%	87.29%	22.21%	68,490
Iteration 5	100.00%	87.29%	22.21%	68,490
Iteration 6	100.00%	87.29%	22.21%	68,490
Iteration 7	100.00%	87.29%	22.21%	68,490
Iteration 8	100.00%	87.29%	22.21%	68,490
Iteration 9	100.00%	87.29%	22.21%	68,490
Iteration 10	100.00%	87.29%	22.21%	68,490

Mean Vaccination				
Base	81.30%	76.80%	19.34%	68,490
Iteration 1	81.25%	76.64%	19.45%	68,490
Iteration 2	81.25%	76.62%	19.46%	68,490
Iteration 3	81.25%	76.61%	19.46%	68,490
Iteration 4	81.25%	76.61%	19.46%	68,490
Iteration 5	81.25%	76.61%	19.46%	68,490
Iteration 6	81.25%	76.61%	19.46%	68,490
Iteration 7	81.25%	76.61%	19.46%	68,490
Iteration 8	81.25%	76.61%	19.46%	68,490
Iteration 9	81.25%	76.61%	19.46%	68,490
Iteration 10	81.25%	76.61%	19.46%	68,490

The base vaccination coverage rate is the raw cluster vaccination rate in the data which excludes children who have died. The vaccination coverage rate in iterations 1-10 corrects for this missing data using the procedure described in the main text.

Table A4: DHS Surveys Included in the Analysis

DHS Survey: Year	DHS Survey: Year
Albania Year: 2008-2009	Central African Republic Year: 1994-1995
Bangladesh Year: 1993-1994	Chad Year: 1996-1997
Bangladesh Year: 1996-1997	Chad Year: 2004
Bangladesh Year: 1999-2000	Colombia Year: 1990
Bangladesh Year: 2004	Colombia Year: 1995
Bangladesh Year: 2007	Colombia Year: 2000
Benin Year: 1996	Colombia Year: 2005
Benin Year: 2001	Colombia Year: 2010
Benin Year: 2006	Comoros Year: 1996
Bolivia Year: 1994	Congo Democratic Republic Year: 2007
Bolivia Year: 1998	Congo (Brazzaville) Year: 2005
Bolivia Year: 2003	Cote d'Ivoire Year: 1994
Bolivia Year: 2008	Cote d'Ivoire Year: 1998-1999
Brazil Year: 1996	Dominican Republic Year: 1996
Burkina Faso Year: 1993	Dominican Republic Year: 1999
Burkina Faso Year: 1998-1999	Dominican Republic Year: 2002
Burkina Faso Year: 2003	Dominican Republic Year: 2007
Burkina Faso Year: 2010	Egypt Year: 1995
Burundi Year: 2010	Egypt Year: 2000
Cambodia Year: 2000	Egypt Year: 2005
Cambodia Year: 2005	Egypt Year: 2008
Cambodia Year: 2010	Ethiopia Year: 2000
Cameroon Year: 1991	Ethiopia Year: 2005
Cameroon Year: 1998	Ethiopia Year: 2011
Cameroon Year: 2004	Gabon Year: 2000
Cameroon Year: 2011	Ghana Year: 1993
Ghana Year: 1998	Lesotho Year: 2009
Ghana Year: 2003	Liberia Year: 2007
Ghana Year: 2008	Madagascar Year: 1997
Guatemala Year: 1995	Madagascar Year: 2003-2004
Guinea Year: 1999	Madagascar Year: 2008-2009
Guinea Year: 2005	Malawi Year: 1992
Guyana Year: 2009	Malawi Year: 2000
Haiti Year: 1994	Malawi Year: 2004
Haiti Year: 2000	Malawi Year: 2010
Haiti Year: 2005-2006	Maldives Year: 2009
Honduras Year: 2005-2006	Mali Year: 2001
India Year: 1992-1993	Mali Year: 2006
India Year: 1998-1999	Moldova Year: 2005
India Year: 2005-2006	Morocco Year: 1992
Indonesia Year: 1997	Morocco Year: 2003-2004
Indonesia Year: 2002-2003	Mozambique Year: 1997
Indonesia Year: 2007	Mozambique Year: 2003
Jordan Year: 1990	Namibia Year: 1992
Jordan Year: 1997	Namibia Year: 2006-2007
Jordan Year: 2002	Nepal Year: 1996

Table A4 – Continued on the Next Page

DHS Survey: Year	DHS Survey: Year
Jordan Year: 2007	Nepal Year: 2001
Kenya Year: 1993	Nepal Year: 2006
Kenya Year: 1998	Nepal Year: 2011
Kenya Year: 2003	Nicaragua Year: 1998
Kenya Year: 2008-2009	Nicaragua Year: 2001
Lesotho Year: 2004	Niger Year: 1998
Niger Year: 2006	Tanzania Year: 2004-2005
Nigeria Year: 1990	Tanzania Year: 2010
Nigeria Year: 2003	Timor Leste Year: 2009-2010
Nigeria Year: 2008	Togo Year: 1998
Pakistan Year: 1990	Turkey Year: 1993
Pakistan Year: 2006-2007	Turkey Year: 1998
Paraguay Year: 1990	Uganda Year: 1995
Peru Year: 1991-1992	Uganda Year: 2000-2001
Peru Year: 1996	Uganda Year: 2006
Peru Year: 2000	Uganda Year: 2011
Philippines Year: 1993	Vietnam Year: 1997
Philippines Year: 1998	Vietnam Year: 2002
Philippines Year: 2003	Zambia Year: 1996
Philippines Year: 2008	Zambia Year: 2001-2002
Rwanda Year: 1992	Zambia Year: 2007
Rwanda Year: 2000	Zimbabwe Year: 1994
Rwanda Year: 2005	Zimbabwe Year: 1999
Rwanda Year: 2010	Zimbabwe Year: 2005-2006
Sao Tome and Principe Year: 2008-2009	Zimbabwe Year: 2010-2011
Senegal Year: 2005	
Senegal Year: 2010-2011	
Sierra Leone Year: 2008	
South Africa Year: 1998	
Swaziland Year: 2006-2007	
Tanzania Year: 1996	
Tanzania Year: 1999	

Note: Demographic and Health Survey data are available from www.dhsprogram.com.